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Advances in hemoglobin disorders - Section 3

New therapeutic approaches for hemoglobinopathies: Pharmacologic agents impacting pathophysiology

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Take Home Messages

- Many trials are currently underway to identify active disease modifying agents in thalassemia and sickle cell disease.
- A clear understanding of the pathophysiology of these disorders has allowed the identification of targets for drug therapy.
- Completion of important trials will rely on commitment of patients and investigators to this process.

Introduction

Until recently the management of sickle cell disease (SCD) and thalassemia was limited to supportive care, preventive measures, transfusions and chelation. The approval of hydroxyurea, a disease modifying agent, for SCD ushered a new era in the treatment of this disorder. In addition to stem cell transplantation and gene therapy approaches, processes known to be involved in the pathophysiology of hemoglobinopathies are now targets for drug development. The induction of fetal hemoglobin production could ameliorate symptoms in SCD and decrease transfusion requirements in thalassemia.[1,2] Approaches specific to sickle cell disease include: the development of anti-sickling agents that increase the oxygen affinity of hemoglobin.[3] Inhibition of adhesion molecules such as of P and E selectin have shown promise in preventing vaso-occlusive crises (V0C), and in decreasing opioid use during a crisis[4-5] (clinical trials for SCD are summarized in Table 1). In thalassemia, pharmacological approaches focused on the improvement of ineffective erythropoiesis and prevention of iron loading[6-7] are in clinical or preclinical phase of development. It should be borne in mind that most of the new agents, which are the topic of this review, are currently under investigation and have not yet been approved for clinical use.

Trials in sickle cell disease

Fetal hemoglobin induction

Induction of fetal hemoglobin(HbF) has been extensively investigated. Higher levels of HbF are associated with lower mortality and amelioration of the complications in SCD.[1] Hydroxyurea acts in large part due to its ability to increase HbF, but the decrease in HbF levels over time may be associated with the decreasing effectiveness of HU. Several potential HbF inducing drugs have been investigated with disappointing results, including butyrates.[1] Understanding the mechanism HbF modulation and the roles BCLL11, MYB and KLF 1 has led to the development of gene editing approaches including the silencing of the repressor BCL11A.[1,2] Pharmacological interventions have focused on DNA methyl transferase inhibitors such as decitabine, a recent study has demonstrated the safety of an oral formulation of this drug given with the inhibitor of cytidine deaminases, tetrahydrouridine.[8] Histone deacetylase inhibitors are also undergoing clinical trial. Recently metformin was found to potentially induce HbF through FOXO3 and this agent is now under investigation in SCD.[1,9] Recent studies have shown that phosphodiesterase 9 (PDE9) inhibitors are associated with increases in fetal hemoglobin and decreased inflammation and two agents have entered clinical trials[10] (Table 1).

Inhibition of sickle polymerization

The sickling process is initiated by the formation of sickle hemoglobin (HbS) polymers upon deoxygenation. The development of molecules that increase the oxygen affinity of HbS may thus prevent the initiation of sickling and the deleterious impact of this process. One such agent is voxeletor, also known as GBT 440. This is an oral agent that has shown activity and a good safety profile and is currently in clinical trials aimed at increasing hemoglobin levels, in patients with sickle cell disease.[3]

Inhibition of adhesion and cell-cell interactions

Early work by Hebbel and colleagues demonstrated that the erythrocyte adherence was a possible measure of severity in SCD.[11] Recently the nonspecific anti adhesion molecule Poloxamer 88 was shown to be ineffective in shortening the duration of painful crises. Specific inhibition of selectins has shown greater promise. Preclinical studies have shown that P selectin inhibition was associated with protection against vaso-occlusion in sickle cell mice. In humans a randomized trial demonstrated that monthly administration of the humanized anti P selectin antibody crizanlizumab, at high dose, led to a decrease in the annual rates of VOC and longer time till the first event.[5] Heparin also can inhibit P selectin mediated cell adhesion and a trial is investigating the

potential of a heparin derivative, without anticoagulant properties, Sevuparin[12] to shorten the duration of VOC if administered early during the onset of pain. The anti E selectin compound GMI-1070, now referred to as Rivipensel, was shown to decrease the use of opioids during VOC[4] and is currently undergoing further investigation.

Anticoagulants and anti-platelet agents

SCD disease has long been known to be a hyper coagulable state, including an increase in activated platelets. Recent studies have focused on anti-platelet agents as well as anticoagulants (Table 1). A large international multicenter placebo-controlled trial failed to show an effect of prasugrel in preventing VOC in children and adolescents with SCD.[13] Nonetheless, this trial opened the way for large trials with other anti-platelet agents, such as ticagrelor, looking at the impact of optimizing levels of platelet inhibition.

Nitric oxide production and antioxidants

The nitric oxide pathway and oxidative stress have also been targets of investigation. Compounds being considered for investigation include arginine, shown to be effective in decreasing use of opioids during VOC,[14], omega 3 fatty acids and glutamine. Recently the FDA approved use of a special formulation of glutamine, Endari, in SCD as a trial showed it to be effective in preventing vaso-occlusive episodes.[15] This is a promising field for investigation and deserves further exploration as indicated in a recent systematic review.[16]

Trials in thalassemia

Agents targeting ineffective erythropoiesis

Ineffective erythropoiesis is a hall mark of the thalassemic marrow. In elegant studies Hermine and colleagues have shown that compounds which bind to trap ligands and prevent activin binding to activin receptor 2 improve erythroid maturation.[7] These studies have served as the basis of a phase 2 trial that showed decreased need for transfusion in thalassemia patients.[1]. A phase 3 trial is ongoing (luspatercept BELIEVE NCT02604433).

Agents targeting iron loading

Increasing hepcidin expression in thalassemic mice decreases iron loading in the liver and improves RBC life span.[18] Approaches to using mini hepcidins are currently in preclinical studies as are ways to increase endogenous hepcidin production.[6]

Agents targeting heme synthesis and alpha beta chain imbalance

Recently it was shown that the drug bitopertin, RO 491738, initially developed as an antipsychotic agent, effects erythropoiesis through glycine transporter 1 inhibition, leading to decreased heme synthesis.[19] This could have a salutary effect on the alpha beta chain imbalance in beta thalassemia. A phase 2 study of the drug is currently underway (NCT0371541).

Conclusion

These are exciting times for investigators and patients with hemoglobinopathies. Several curative and therapeutic approaches are under development. In sickle cell disease the challenge is now to prioritize trials such that they accrue the required number of patients and to evaluate meaningful end points. The way forward will require the collaboration of scientists, clinicians and patient groups to achieve these aims.

Table 1. **Selected clinical trials in sickle cell disease. Adapted from Ware *et al.* Lancet 2017;390:311-23; with permission. Clinicaltrials.gov accessed March 13, 2018.**

	Treatment	Phase	Endpoint measure	Enrolment
NCT01245179	Panobinostat	1	Safety, tolerability	Active
NCT01685515	Decitabine & Tetrahydrouridine	1	Safety, tolerability	Recruiting
NCT02114203	PDE9 Inhibitor	1	Safety, tolerability	Completed
NCT03401112	PDE9 inhibitor Imara	2	Effectiveness	Recruiting
NCT02285088, NCT02567682	GBT440	1	Safety, tolerability	Recruiting
NCT02712346	Ambrisentan	1	Safety, tolerability	Recruiting
NCT01566890, NCT01788631	Regadenoson	2	Vaso-occlusion	Completed
NCT01891292	Enalapril & N-acetylcycteine	2	Renal	Recruiting
NCT01895361	SelG1	2	Vaso-occlusion	Completed
NCT02098993	Unfractionated heparin	2	Acute chest syndrome	Recruiting
NCT02482298	Ticagrelor	2	Vaso-occlusion	Recruiting
NCT02373241	Losartan	2	Nocturnal BP	Recruiting
NCT02411708	Carboxyhemoglobin	2	Vaso-occlusion	Recruiting
NCT02515838	Sevuparin	2	Vaso-occlusion	Recruiting
NCT02536170	L-arginine	2	Pain	Recruiting
NCT02672540	Carboxyhemoglobin	2	Vaso-occlusion	Not open
NCT01737814, NCT02449616	Poloxamer 188	3	Vaso-occlusion	Completed
NCT02187003	GMI-1070	3	Vaso-occlusion	Recruiting
NCT03285178	Soluble guanylate cyclase stimulator IW1701	2	Safety	Recruiting
NCT02604368	Omega 3-fatty acids	3	Vaso-occlusion	Recruiting

References

*1. Paikari A, Sheehan VA. Fetal haemoglobin induction in sickle cell disease. Br J Haematol 2018;180: 189–200.
An excellent and up to date review on fetal hemoglobin induction in sickle cell disease.

*2. Thein SL. Molecular basis of thalassemia and potential therapeutic targets. Blood Cells Mol Dis 2018;70:54-65.
An extensive review of potential therapeutic modalities for thalassemia

3. Estepp JH. Voxeletor (GBT440), a first-in-class hemoglobin oxygen affinity modulator, has promising and reassuring preclinical and clinical data. Am J Hematol 2018 93:326-9.

4. Telen M J, Wun T, McCavit TL, et al. Randomized phase 2 study of GMI-1070 in SCD: reduction in time to resolution of vaso-occlusive events and decreased opioid use. Blood 2015;125:2656–64.

*5. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med 2017;376:429-39.
A randomized, well designed clinical trial, which demonstrated the efficacy of selectin inhibition, for the prevention of vaso-occlusive crises. Crizanlizumab may soon enter clinical use.

6. Taher AT, Weatheral, DJ, Cappellini MD. Thalassaemia. Lancet 2017;391:155-67.

*7. Dussiot M, MAciel TT, Fricot A, et al. An Activin receptor IIA ligand trap corrects ineffective erythropoiesis in B thalassemia. Nat Med 2014;20:398-407.
An important work from a group that defined potential therapeutic interventions to improve ineffective erythropoiesis.

8. Molokie R, Lavelle D, Gowhari M, et al. Oral tetrahydrouridine and decitabine for non-cytotoxic epigenetic gene regulation in sickle cell disease: A randomized phase 1 study. PLoS Med 2017;14.

9. Shehaan VA, Weiss MJ, Zhang Y, et al. Metformin induction of fetal hemoglobin. Blood 2017;130:359 .

10. Almeida CB, Scheiermann C, Jang JE, et al. Hydroxyurea and a cGMP-amplifying agent have immediate benefits on acute vaso-occlusive events in sickle cell disease mice. Blood 2012;120:2879-88.

11. Solovey A, Lin Y, Browne P, et al. Circulating endothelial cells in sickle cell anemia. N Engl J Med 1998;338:1162-3.

12. Telen MJ, Batchvarova M, Shan S, et al. Sevuparin binds to multiple adhesive ligands and reduces sickle red blood cell-induced vaso-occlusion. Br J Haematol 2016;175:935-48.

13. Heeney MM, Hoppe CC, Abboud MR, et al. A Multinational trial of prasugrel for sickle cell vaso-occlusive events. N Engl J Med 2016;374:625-35.

14. Morris CR, Kuypers FA, Lavricha L, et al. A randomized placebo controlled trial of arginine therapy for children with sickle cell disease hospitalaized with vaso-occlusive pain episodes. Hematologica 2013;98:1375-82.

15. L-glutamine (Endari) for sickle cell disease. Med Lett Drugs Ther 2018;60:21-2.

*16. Sins WR, Mager DJ, Davis SCAT, et al. Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review. Blood Adv 2017;1:1598-616.
An extensive evaluation of published trials in sickle cell disease that identified areas of promise for future investigation.

17. Piga A, Perrotta S, Melpignamo A, et al. Luspatercept decreases transfusion burden and liver iron concentration in regularly transfused adults with beta thalsemia. Haematologica 2016;101:338-9.

18. Casu C, Oikonomidou PR, Chen H, et al. Minihepcidin peptides as disease modifiers in mice affected by beta thalassemia and polycythemia vera. Blood 2016;128:265-76.

19. Winter M, Funk J, Körner A, et al. Effects of GlyT1 inhibition on erythropoiesis and iron homeostasis in rats. Exper Hematol2016;44:964-74.

20. Ware RE, Montalembert MD, Tshilolo L, Abboud MR. Sickle cell disease. Lancet 2017;390:311-23.